## REMARKS

Status of the Claims:

Originally filed claims 1-47 were previously canceled and claims 48-81 added by amendment. Claim 63 was canceled in a reply mailed March 25, 2003, leaving claims 48-62 and 64-81 pending in the case.

Claims 48-62 and 64-81 are currently canceled.

Claims 82-95 are added.

Problem to be Solved:

The general problem to be solved is to increase cloning efficiency and nuclear transfer totipotency.

The Invention:

The invention is a series of selections and manipulations that result in improved cloning efficiency through use of somatic cells, adult or aged, obviating the need to use embryonic stem cells. Culturing the somatic cells under conditions of serum starvation provides improved fusion and cleavage rates and blastocyte formation, resulting in high pregnancy rates when embryos are transferred into a recipient. Use of the new method will enable increased efficiency in producing cloned animals, as exemplified by the production of healthy, normal cows.

Double Patenting

Claims 53, 54, 56, 57, 65, 67, 68, 71, 73, 74, 77, 79 and 80 are provisionally rejected under an obvious-type double patenting rejection over claims 1-25, and 30-31 of copending Application No.10/274,432 as not patentably distinct although not identical.

Applicants believe claims 82-95 are patentably distinct and respectfully request deferral of a response to this rejection until the newly presented claims have been examined.

Rejection of Claims 53-58, 71-75 and 77-81 and claims 65-69 under 35 U.S.C. §102(b)

Claims 53-58, 71-75 and 77-81 stand rejected under 35 U.S.C. §102(b) as anticipated by Cibelli, *et al.* and claims 65-69 as anticipated by Plump, *et al.*

With respect to claims 65-69, the Action takes the position that the "product" clone is virtually the same as a clone produced by similar methods, if not the same method. Applicants have reformulated additional claims to more clearly distinguish their novel method by which the clones may be obtained. In view of the added claims, applicants believe that the rejection predicated on the Plump, *et al* reference is moot.

Applicants have also replaced claims 53-58, 71-75 and 77-81, rejected as anticipated by Cibelli, *et al.,* with claims more particularly focusing on the direct results obtained by the novel method, placing emphasis on the substantially improved particular results observed. Applicants respectfully submit that the Action's rejections have been overcome.

Rejection of claims 48-62 and 64-81 under 35 U.S.C. §103(a)

Claims 48, 50, 60, 62 and 76 stand rejected and subsequently amended claims 49, 51-59, 61, 64-75 and 77-81 are rejected under 35 U.S.C. §103(a) as unpatentable over Cibelli, *et al.,* Plump, *et al.*, and Arbones, *et al.* The Action relies on Arbones, *et al.* to show that one could use other than embryonic stem cells for effective genetic manipulation (*e.g.,* myoblasts) and implies that once use of somatic cells is shown to be feasible, one might expect that such cells, given a few doublings to accomplish genetic manipulations, could be used to get cloned animals, given the state of the art in cloning.

Applicants agree that Arbones, *et al.* is concerned with gene targeting and that they performed test experiments using embryonic stem cells, and later with myoblasts. Applicants have carefully studied this reference and note, firstly of course, that the myoblast cells were not used to make cybrids, much less embryos or clones. Secondly, the paper seems to be concerned with cell transformations via gene targeting and shows that with one gene they can achieve efficient targeting. One presumes that the modifications discussed would be more directed to developing gene therapy methods than cloning. Finally, the scientists do not show long-term multiple targeting.

In combining the references, the Action takes the position that the steps Applicants have proposed for their cloning method are known and have been practiced.

Applicants submit that the claims currently presented clearly show that improved success in obtaining an end result (*i.e.* the clone) is due not only to use of an adult somatic cell but also in large part to specific culture conditions (see new claim 82) so that when transferred into donor cells, the produced blastocytes will result in a high rate of pregnancy in recipient animals. Thus Applicants' selection of mature cells and development of special culture conditions results in significant improvements in several steps used in cloning or in longer term multiple gene manipulations.

Of interest also is Applicants' finding that aged somatic cells (from a 17-year old bull) can be used to produce clones. Although Arbones, *et al.* made use of myoblasts from 14-day old mice, one would still likely be surprised that cells from a very old mammal could be used. While Applicants do not purport to relate mouse age to cow or human age, a 14 day old mouse, assuming the average life-span of 1.5 years, is less than 3% of its lifetime so that its cells can be considered young, not mature and certainly not aged. A 17-year old bull is close to the end of its normal "late-teens" life span.

Added Claims:

The added claims replace all previously pending claims and are intended to more clearly claim the subject matter Applicants consider to be the invention. The added claims are supported throughout the specification; in particular, at Table 4 showing percent pregnancies; page 39, lines 8-14 referring to number of passages for serum-starved cells; and page 38, lines 2-5 describing the effect of donor cell passage number on cloning competence and use of adult somatic cells.

Conclusion:

Applicants submit that claims 82-95 are in condition for allowance and such action is respectfully requested.

Reconsideration of the application is respectfully requested.

Respectfully Submitted,

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